

REMARKS

I. Telephonic Interview Conducted July 28, 2011

Applicants thank the Examiner for taking the time to discuss the outstanding office action and the pending claims. Applicants, represented by William K. Merkel, Ph.D. and Lance M. Shaner, Ph.D., and Examiner Winston Shen addressed issues relating to *prima facie* obviousness, but agreement was not reached.

II. The Office Action

Claims 1-62 are currently pending in the application. Claims 1-7, 9, 30-36, 38, and 39 are under examination, and claims 8, 10-29, 37, and 40-62 are withdrawn. In the Office Action, the Examiner rejected the pending claims under 35 U.S.C. § 103(a) over Rafii et al. (U.S. Pat. Pub. No. 20040071687; hereinafter “Rafii”) in view of Fisher et al. (*Biochem*, 41(26):8289-97 (2002); hereinafter “Fisher”), Mohle et al. (*Blood*, 91(10):3283-91 (2001); hereinafter “Mohle”) and Kollet et al. (*Blood*, 97(10), 3283-91 (2001); hereinafter “Kollet”). Reconsideration of these rejections is respectfully requested.

III. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn.

The Examiner rejected claims 1-7, 9, 30-36, 38, and 39 under 35 U.S.C. § 103(a) as assertedly obvious over Rafii in view of Fisher, Mohle and Kollet. This rejection is respectfully traversed for the reasons set forth below.

Claim 30 is an exemplary independent claims directed to a method of generating stem cells suitable for transplantation. The method comprises (a) collecting stem cells; (b) exposing said stem cells to an exogenous matrix metalloprotease (MMP) or an active portion thereof; and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the MMP or an active portion thereof, to thereby generate stem cells suitable for transplantation.

In the Office Action, the Examiner cited Rafii for the teaching that “MMP-9 promotes release of stem cell active cytokines, thereby promoting expansion of quiescent stem cells, and this novel concept lays the foundation of developing strategies where

activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells that may ultimately be used for organ-regeneration and tissue vascularization.” Office Action, p. 7. The Examiner acknowledged that Rafii does not teach treatment of stem cells with exogenous matrix metalloprotease. *Id.* at p. 9. Of significance, Rafii does not disclose or suggest that exposure of stem cells to a matrix metalloprotease increases CXCR4 expression therein.

The Examiner cited Fisher for disclosing that MMP-9 up-regulation can be achieved by expression of exogenous MMP-9 protein from a polynucleotide or by addition of exogenous MMP-9 protein to cells.

The Examiner cited Mohle “[w]ith regard to the limitations [relating to] mobilized stem cell[s] having increased CXCR4 levels recited in claims 1, 2, 30, and 39....” Office Action, p. 10. Mohle discloses that CXCR4 is the receptor for SDF-1 and stem cells mobilize in response, or chemotax, to an SDF-1 gradient. It is not disputed that CXCR4 is the receptor for SDF-1 or that stem cells chemotax up an SDF-1 gradient. Of significance to the pending claims, Mohle does not disclose exposing stem cells to an exogenous matrix metalloprotease and isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof.

The Examiner cited Kollet “[w]ith regard to the limitations [relating to] the expression of markers of mobilized hematopoietic stem cells recited in claims 5-7 and 34-36....” Office Action, p. 10. The Examiner noted that *ex vivo* cytokine-stimulated cord blood CD34⁺CD38⁺ cells had increased CXCR4 expression and improved migration capacities responsive to a gradient of SDF-1, and that primitive CD34⁺CD38^{-/low} cells express higher levels of CXCR4 than CD34⁺CD38^{+/high} cells. Kollet identified the *ex vivo* cytokine used to stimulate cord blood stem cells, and that cytokine is SCF. The pending claims, however, recite that the stem cells are exposed to a matrix metalloprotease, not to SCF. Kollet does not teach treatment of stem cells with a matrix metalloprotease and isolation of stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease.

To establish a *prima facie* case of obviousness, the Office must establish that the art disclosed or suggested each claim-recited element, that there is a reason to modify a teaching or to combine teachings of multiple references, and one of skill must have a reasonable expectation of success in practicing the claimed subject matter. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007).

The Examiner has failed to establish a *prima facie* case of obviousness for the following reasons. First, the Examiner has not established that the cited references disclose or suggest each claim-recited element. Specifically, the Examiner has not established that the prior art discloses or suggests exposing stem cells to an exogenous matrix metalloprotease and isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease. U.S. patent claims, including the instant method claims, are not simple collections of unrelated structural features. While structural features are required in U.S. patent claims, the claims must also establish how the structural features relate to each other to yield a cohesive whole.

The Examiner has relied on Rafii and Fisher as teaching that cytokine-induced upregulation of MMP-9 led to increased stem cell mobility. The Examiner also relied on Kollet and Mohle as teaching that cytokine-stimulated stem cells showed increased expression of CXCR4. These two features of, e.g., claim 30 are never related by the Examiner. Rafii and Fisher address MMP-9, but not CXCR4; Kollet and Mohle address CXCR4, but not MMP-9. The Examiner has not established, in the cited art or knowledge in the art, that MMP-9 and CXCR4 are related in any way, and for this reason, the subject matter of the rejected claims cannot be obvious under § 103(a) over the cited art.

Stated, alternatively, when assessing the differences between the prior art and the claimed invention, the Examiner must consider whether the claim as a whole would have been obvious. See M.P.E.P. § 2141.02(I). The Examiner relied on Rafii and Fisher for disclosure relating to an MMP-9 signaling pathway and stem cells generally and he relied on Mohle for “increased CXCR4.” As noted above, Mohle discloses that CXCR4 is the receptor for SDF-1 and that stem cells chemotax in response to an SDF-1 gradient. Kollet discloses that *ex vivo* cytokine-stimulated, i.e., SCF-stimulated, cord blood cells CD34⁺CD38⁺ cells had increased CXCR4 expression. Mohle and Kollet neither disclose nor suggest exposing

stem cells to a matrix metalloprotease and don't disclose or suggest any effect on CXCR4 expression attributable to exposing stem cells to a matrix metalloprotease. Thus, the Examiner has not established that the cited references, alone or in any combination, disclose or suggest exposing stem cells to a matrix metalloprotease and isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease, as recited in independent claim 30. Accordingly, the rejection of the claims as obvious under 35 U.S.C. § 103(a) has been overcome and should be withdrawn for at least this reason alone.

Second, the Examiner has not provided a reason to modify or to combine teachings of the cited references to arrive at the claimed invention. In an effort to meet the requirement that a reason for modifying or combining cited references must be provided, the Examiner provided summary teachings from the art as a basis for concluding that a person of skill in the art would have been motivated to combine the teachings of Rafii, Fisher, Mohle and Kollet. The M.P.E.P. provides that even if the references teach that all aspects of the claimed invention were individually known in the art (a proposition that is disputed above), this is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. M.P.E.P. § 2141.01(IV) (citing *Ex parte Levingood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) and *KSR*, 127 S.Ct. at 1741, “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”). The Examiner provided separate summaries of the facts asserted in the four cited references. The Examiner did not provide a rationale for why it would have been obvious for a person of ordinary skill in the art to arrive at the claimed method of generating stem cells suitable for transplantation by collecting stem cells, exposing the stem cells to a matrix metalloprotease, and isolating stem cells with increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease. The Examiner is selectively choosing portions of the cited references without providing a reasonable basis for combining their teachings. Applicants are aware that, in a sense, all examination of claims involves hindsight reconstruction. Where there is no reason provided to combine references, as here, the hindsight reconstruction is impermissible. The Examiner has not established that a person of skill in the art would have had a reason to combine the teachings of the cited references to arrive at the claimed invention.

Finally, the Examiner has not established that there would be a reasonable expectation of success in combining the cited references to arrive at the claimed invention. To establish a *prima facie* case of obviousness, the Examiner must establish that a person of ordinary skill in the art would have had a reasonable expectation of success in combining the cited references to arrive at the claimed subject matter. Without first establishing that the prior art discloses or suggest all elements of the claim and that there was a reason to combine teachings in the prior art, there can be no reasonable expectation of success. The Examiner supported and asserted a reasonable expectation of success by again listing summary teachings from the art and stating in a conclusory manner that there would have been a reasonable expectation of success in view of the teachings of Rafii, Fisher, Mohle and Kollet. The Examiner did not attempt to provide any explanation for why there would have been a reasonable expectation of success other than to directly quote the cited references. Both Rafii and Kollet fail to teach exposure of stem cells to MMP-9 and the effect on CXCR4 expression. Neither Fisher nor Mohle disclose or suggest that exposing stem cells to a matrix metalloprotease would upregulate CXCR4 expression. Thus, a person of skill in the art would not have been able to predict that exposure of collected stem cells to a matrix metalloprotease would increase CXCR4 expression, based on the cited references, without using the Applicant's specification as an impermissible hindsight guide to reconstruct the invention. Thus, there could have been no reasonable expectation of success in arriving at the claimed subject matter by modifying the teachings of the cited references. Accordingly, a *prima facie* case of obviousness has not been established for any of the rejected claims. Consequently, the rejection of claims 1-7, 9, 30-36, 38, and 39 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

IV. Conclusion

In view of the above amendments and remarks, Applicants believe that the pending application is in condition for allowance. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions that might be efficiently resolved in that manner.

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Respectfully submitted,

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